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Drug discovery: lessons from evolution

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A common view within the pharmaceutical industry is that there is a problem with drug discovery and we should do something about it. There is much sympathy for this from academics, regulators and politicians. In this article I propose that lessons learnt from evolution help identify those factors that favour successful drug discovery. This personal view is influenced by a decade spent reviewing drug development programmes submitted for European regulatory approval. During the prolonged gestation of a new medicine few candidate molecules survive. This process of elimination of many variants and the survival of so few has much in common with evolution, an analogy that encourages discussion of the forces that favour, and those that hinder, successful drug discovery. Imagining a world without vaccines, anaesthetics, contraception and anti-infectives reveals how medicines revolutionized humanity. How to manipulate conditions that favour such discoveries is worth consideration.

Drug discovery as an evolutionary process

Drug development has features in common with evolution. The classification system of pharmacology echoes the taxonomy of flora and fauna. How certain compounds become successful medicines, from the myriad potential candidate molecules, involves a selection process with a high rate of attrition. Though new molecules do not arise from reproduction, many are modifications of earlier designs with products referred to as first, second or third generation. Variation, a key to evolution, is not in short supply. Between 1958 and 1982 the National Cancer Institute in the USA screened natural products for activity that included 180 000 derived from microbes, 16 000 from marine organisms and 144 000 from plants. A major pharmaceutical company may hold a library of over 2 million compounds available to screen for biological activity.

To move from this vast range of variation to a profitable medicine with a favourable risk benefit depends upon successful selection. Extinction is a common theme in drug innovation, making pessimism rife. The disappointed investor, or industry employee, may witness a fortune disappear without spawning a useful molecule, let alone the elusive blockbuster. Academics may toil for years without a patent. Conferences on innovation may generate fashionable terms, but little that is tangible.

Here forces that apply to the selection process that mould drug discovery are listed under seven headings and the potential for their positive manipulation is discussed.

Funding

Funding is the oxygen and glucose of research. The biggest sums lie with the pharmaceutical industry. The annual turnover in 2009 of the top four pharmaceutical companies ranged between £19 and £33 billion. Annual world pharmaceutical sales are approximately £250 billion. Of these sums, 14% is spent on research. This splits into some 12% on research to provide data that define a place in the market in order to justify a re-imbursement recommendation from national health technology evaluations and 2% on medicines discovery. The only sizeable non-industry source of funds is the US National Institutes of Health, with an annual budget of some £20 billion. In the UK, the combined annual budget for the Medical Research Council, Wellcome Trust and Cancer Research is about £1 billion. The European Innovative Medicines Initiative annual budget is less than £0.2 billion.

Deciding how to spend these large sums involves a tricky interaction between the inventor and the investor, sufficiently awkward for some to think it analogous to mating porcupines. The delicate dance is illustrated by James Watt's correspondence with his first venture capitalist, John Roebuck, in 1765 [1]. At the time Watt was designing many of the key steam engine advances that supported the Industrial Revolution, yet he struggled to maintain a source of funding and had to overcome Roebuck's resistance to invest. Such a challenging interaction is common in pharmaceutical development, where the expertise of the investor may not overlap with the

expertise of the scientific proposer. Watt's attempts to persuade Roebuck to part with his money echo today when academics apply for grants and industry scientists defend investment.

There seems to be more than enough funding spent on research at present. Many key advances over the past 60 years were made by research groups of less than 50 scientists, small by current industry standards. Total research funding has never been higher and to explain the current lack of innovation we need to look elsewhere.

Progress and the Red Queen Hypothesis

Progress in drug development is slow and seems to be getting slower.

The number of applications assessed by US and EU regulators for new active chemical and biological compounds has fallen from 131 in 1996, to 72 in 2003 and 48 in 2009. The number of approvals from the Food and Drug Administration (FDA) at the same time points were 56, 27 and 25 [2]. This decline brings to mind endangered species, where it becomes important to identify deteriorating environments to prevent extinction [3]. Though tougher regulation is often cited as contributing to a deteriorating environment, the approval rate in the EU for submitted applications has never been higher, being 60% in 2009, compared with 40% in 1996 and 29% in 2003 [4].

Evolutionary biologists borrowed the Red Queen's character from Lewis Carroll's Through the Looking Glass to form a hypothesis based on the Queen's claim that it takes all the running you can do to keep in the same place. Parallel evolutionary advances in prey and predator keep such systems in balance, analogous to an arms race [5]. An unmatched evolutionary advance in the speed of the predator might lead to the extinction of the prey and hence the predator.

Many involved in drug discovery consider the regulator as predatory. However advances in science that increase our ability to treat diseases have been matched by similar advances in our understanding of toxicity. The more we know about medicines and disease, the more the regulator needs to know about toxicity to avert public health disasters. This is analogous to the technological advances that bring society many benefits, yet also have the potential for greater destruction from better weapons [6]. We should not be surprised that developments in science that enhance therapeutic efficacy will be balanced by similar advances in the assessment of safety.

Medicines entering a competitive market often require large-scale, long-duration and expensive phase 3 trials, funded by industry, in order to justify re-imbursement. Such huge databases are not at the behest of the regulator. Tougher regulations do not seem to kill good drugs, provided that the expertise of the regulator at least matches that of the innovator. Excessive regulation might affect phase 1 and 2 academic studies, if not backed by high quality review. The US Drug Amendments Bill of 1962 aroused opposition to perceived over regulation. Though this bill was a laudable response to the thalidomide disaster, it also required the US Food and Drug Administration (FDA) to evaluate all clinical trial protocols, ensuring preclinical toxicology is adequate before starting human studies. Despite initial reassurance from the FDA's Frances Kelsey that it would not interfere with competent academic investigations, many in the National Institutes of Health (NIH) considered that FDA intervention was not backed by sufficient scientific assessment expertise [7]. This debate resurfaced with similar criticisms, by Morris Brown, of the 2004 EU Clinical Trial Directive [8].

Red tape does not explain the recent drop in drug innovation, particularly as the number of applications for approval has fallen, whereas the approval rate remains high.

Individual success

When defining best practice it is useful to review past success and for medicines research three individuals stand out. These scientists, Gertrude Elion, James Black and Akira Endo, were products of their surroundings, stood on the shoulders of giants and had many collaborators. Nonetheless their personal contributions to therapeutics were heroic, illustrating that periods of rapid acceleration in drug discovery evolution are feasible.

Gertrude Elion, 1918–99, shared the Nobel prize for Physiology and Medicine in 1988 with George Hitchings and James Black [9, 10]. The committee commented that she deserved the prize for any one of her many discoveries. These included diaminopurine in 1948 as a lead molecule with anti-cancer, anti-bacterial and anti-viral activity, pyrimethamine for malaria in 1950, thioguanine, 6-mercaptopurine and the first remission of childhood leukaemia in 1953 and the anti-bacterial trimethoprim in 1956. Azathioprine in 1957 led to the first kidney transplant in 1962 and opened the whole field of immunosuppression and organ donation. Allopurinol for gout followed in 1963. Aciclovir was the first licensed antiviral in 1997 and opened the door for future drugs for AIDS, where many researchers were trained by her.

James Black, 1924–2010, developed a logical approach to drug development whereby splitting receptors into subtypes with robust laboratory assays led to new medicines which had a more specified target [11]. This technology was applied first to adrenoceptors leading to β-adrenoceptor blockers and the discovery of their benefit in cardiovascular disease. Subsequent work on histamine receptors revolutionized the treatment of peptic ulcers with the introduction of the first H_2-receptor antagonist antacid.

Akira Endo, born in 1933, received the 2006 Japan Prize for his meticulous work screening 6000 compounds from fungi for their potential to inhibit HMG CoA reductase [12]. This led to the first statin. The distribution of his lead compound to collaborators determined many subsequent fortunes within the pharmaceutical industry.

These three individuals illustrate what can be achieved with groups of 50 or fewer researchers. A common theme is their knowledge of chemistry and sheer dedication. All had a strong wish to improve the lot of their fellow man and all worked within the pharmaceutical industry. What is most surprising is how few researchers, investors and decision makers are aware of these achievements. Fortunately the benefit of co-operation between scientists and clinicians is a concept that is back in favour, re-branded as translation [13]. Greater recognition of these individuals, together with an analysis of the reasons for their success, seems obvious for anyone interested in drug discovery and an opportunity to put current research into perspective.

Meteoric upheaval

Large-scale events can induce rapid evolutionary change, such as the meteorite that triggered mass species extinction 65 million years ago. A positive impact on drug discovery was the American military draft during the time of the Korean and Vietnamese wars, which indirectly gave rise to the Berry Plan of 1954–74 [14]. Under this scheme the brightest US medical graduates, often referred to as the Yellow Berets of the Battle of Bethesda, were allowed to undertake 2 years' draft military service by applying to the Public Health Service for an NIH position. The Associate Training Program became highly prized. At the peak in 1963 there were 1464 applicants for 53 posts, with Harvard alumni being the most successful applicants. By 1974, at the end of the program, NIH was unable to fill its Associate quota for the year, as lifting the threat of a military draft caused a dramatic fall in applications [15].

The Associate Program provided a tremendous opportunity for bench-to-bedside clinical research and started the careers of so many who contributed to the NIH's 'Golden Age of Research and Development' [7]. Most of the major leaders of drug discovery took part. As late as 1998 24% of the professors of medicine at Harvard Medical School and 20% at Johns Hopkins University Medical School were ex-NIH associates [15]. The waning influence of the Berry Plan coincided with a rise in funding for genetics. As genetics prospered, clinical pharmacology declined. In the UK the number of consultant clinical pharmacologists reached a peak in 1992, but then halved over the next 10 years [16].

The crowning achievement of genetics research was the human genome project in 2000. This monumental milestone attracted accolades from Heads of State and special editions of leading journals. The limelight led many in drug research to predict major genetics based therapeutic advances, an advantage for fund and grant raising, given the high profile publicity that genetics research attracted. Yet few medicines have arisen from this research, taking into account the magnitude of the investment [17].

Remarkable advances in molecular haematology identified the simple biochemical causes of many haemoglobinopathies. Yet even monogenic diseases may be complex because of the influence of modifiers on the translation of genotype to phenotype [18]. In 1989 the major genetic abnormality which underlies the cystic fibrosis transmembrane conductance regulator (CTFR) protein deficiency in cystic fibrosis (CF) was discovered. Despite predictions of simplicity, the inheritance proved to be manifold [19]. There are now some 1700 known mutations of the *CTFR* gene, though not all cause the condition. Multiple inherited and environmental genetic modifiers are additional influences on the expression of the disease.

Though genetics produced useful tests, such as CTFR carrier status for CF, expansion of the new technology for common diseases has been disappointing. Despite the enthusiasm for a new era of personalized medicine based on an individual's genome [20], getting patient benefit from the genome remains a challenge. A simple illustration of predicting phenotype from genotype is the caterpillar that turns into a butterfly whilst retaining the same genome; knowing the complete genetic sequence cannot predict the morphology. This limitation is important for the genetics of complex disorders. Using the many endocrine systems involved in hypertension as an example, just one hormone may have different genes controlling its production, metabolism, excretion, receptors and second messenger system. How these genes are translated depends upon a host of genetic and environmental modifiers. There is no simple genetic cause for most diseases.

The NIH has responded to the genetics revolution by investigating rare diseases where single gene malfunction leads to the human equivalent of the genetic knock-out animal model. For Gaucher's, Niemann-Pick, Fabry and Tay-Sachs diseases these studies open the door to therapeutic revolutions in replacement treatments [21]. Though these are great advances, they do not justify personalized medicine for common diseases. The large sums invested recently in proteomics have added little in terms of medical applications [22], beyond the older technologies of synthesizing endogenous proteins and monoclonal antibodies.

The best bet for genetics research remains cancer therapeutics. The discovery of the oncogenic genetic translocation, the Philadelphia chromosome in leukaemia, stimulated the search for cancer biomarkers and therapeutic targets [23, 24]. This aspect of genetics continues to expand and there will be many additions to the current list of cancer biomarkers such as BRAC1, BRAC2, erbB2, EGFR, K-Ras or B-RAF. To treat the cancers identified by

biomarkers will still depend on the ability to develop non-biological new drugs, such as the tyrosine kinase inhibitors.

Education

Drug discovery requires specialist knowledge and three areas have stood out for almost a century – chemistry, pharmacology and clinical pharmacology [25]. To this should be added biology, given the number of drugs from vaccines, blood products, proteins and monoclonal antibodies, together with advances in the detection of biomarkers.

The influence of chemistry is illustrated by the three innovators referred to above, who were all first-class chemists. The common chemistry of purine metabolism underlies the string of Gertrude Elion's successes. As she started her career the importance of biochemistry to drug metabolism and the expanding field of enzymology was apparent. This is reflected in Louis Katz's advice to a young to Al Sjoerdsma in 1951 that 'you've got to get into biochemistry, forget physiology' [7]. As the president of the American Association for the Advancement of Science, Chauncey Leake noted in 1961 that pharmacology could not develop until the rise of modern chemistry [26].

Most large pharmaceutical companies trace their roots to a chemical company origin. A cause and effect has been postulated for the decline in chemistry education and the decline in the number of UK pharmaceutical companies and chemical industries [27]. A reminder of the lack of chemistry in current drug development is illustrated all too often by deputations from industry discussing a development programme where each member of the team knows the market share forecast, but none can draw the new medicine's chemical structure. Linking academia to industry assists innovation and being close to a highly-ranked chemistry department can double the number of private pharmaceutical laboratories and increase the number of chemical industries [28]. The recent interest in nanotechnology is welcome [29], but much of chemistry remains underfunded.

Though attempts have been made to resuscitate a similar scheme for medical graduates [30], the Berry Plan remains unique. Its special contribution to medicines development needs recognition and some method found of compensating for its loss. National institutions and industry should work to ensure an adequate education system for chemistry, pharmacology, clinical pharmacology and biology.

Communication, secrecy and patents

Altruism has long been popular with philosophers and academic societies. In his book 'The New Atlantis' (1627), Francis Bacon outlined many of the ideas that underlie modern universities with the emphasis on altruism and centralization. There would be a Solomon's House of Knowledge; Utopia would prevail; science and technology should be supported by a Royal College of Research. Altruism was also promoted by the Royal Society of Arts, which between 1754 and 1784 awarded 6000 prizes to inventors, yet did not recognize the importance of patents until 1845 [1]. The idea of the common good continues to be attractive, such as the lack of a patent for the invention of monoclonal antibody technology. A recent article in the New York Times, on sharing biomarker data in Alzheimer's disease, quoted researchers as saying 'No one would own the data. No one could submit patent applications' [31].

In contrast to altruism is the philosophy of ownership of intellectual property. Greek, Roman, Venetian and Tudor dynasties all awarded market protection to manufacturers (advances in glass technology is a common example) by issuing an open, or 'patent', letter from the ruler. UK patent law arose from a debate about the importation of playing cards that led to the Statute on Monopolies recognizing intellectual property in 1624. The concept developed with the UK Copyright Law of 1710 and the US Patent Act of 1790. Above the old US Patent Office, now the White House Visitor Center, is carved a quotation from the only US president to hold a patent, Abraham Lincoln, 'The patent system added the fuel of interest to the fire of genius' [1].

The potential for academic research to generate patents and hence attract greater funding was facilitated by the US Bayh-Doyle Act of 1980. This was extended to allow the participation of US federal laboratories, including the NIH, by the Federal Technology Transfer Act 1986 [32] and now much is made of translational research. Despite its long history, the patent system remains complex and is in need of international co-ordination, particularly in Europe [33]. Simplification of the patent application system would greatly aid academic groups who have limited funding.

The conflict between the need for commercial secrecy and making all knowledge available for the public good requires communication systems that can accommodate both to some extent. Good communication is an essential catalyst to innovation. Establishing the Royal Society in 1660 allowed a remarkable exchange of ideas from leading innovators across a range of science from Robert Hooke, Robert Boyle, Christopher Wren to Issac Newton. During the 18th century Scottish Enlightenment, James Watt (steam engine) and Adam Smith (economic theorist whose profile adorns the £20 note) were both in Glasgow (population only 14 000 in 1724) [1]. Both had regular contact with James Lind, who carried out the ground breaking controlled trial of citrus fruit for scurvy that is often quoted as a cornerstone of clinical pharmacology [34]. All three encouraged each other's creativity and open approach to experimentation.

The major advances of the British Industrial Revolution were made possible by the monthly meeting of a mere dozen leading scientists and industrialists during The Enlightenment in England. Meeting on the day of the full moon they were known as the Lunar Men. The members, who included Darwin's grandfather, exchanged ideas that revolutionized industries involving iron, coal, canals, pottery, chemistry and mass production [35]. Well aware of commercial sensitivity and patent protection, they were nonetheless able to discuss a formidable range of topics [35]. The tiny size of these meetings contrasts with current medical conferences of 20 000 or more, or pharmaceutical companies with 100 000 employees. History shows that scientists who are isolated by confidentiality agreements can be more productive when allowed a freer exchange of ideas, provided that intellectual property is respected. Internet search engines are now a major contribution to information availability and the net helps rapid communication. Greater interaction can be accommodated without jeopardizing patents, which remain crucial to ensure that promising compounds will be funded when the time comes to pay for clinical research.

Commerce and marketing

Medicines, like other mass produced goods, require a sophisticated system of manufacturing and marketing; commercial rules apply to any large industry. Academic success and commercial success may go hand in hand, but successful commercial species can be selected in the absence of academic success and *vice versa*. James Black's cimetidine, launched in 1975, became the world's largest selling prescription drug and was both an academic and commercial success. By 1988 cimetidine's top commercial spot was taken by the longer lasting me-too drug ranitidine. This in turn was replaced by the protein pump inhibitor omeprazole. Hundreds of trials were conducted to show that proton pump inhibitors are marginally more effective than H_2-receptor blockers [32]. To cope with the loss of revenue of omeprazole coming off patent, Astra launched 'Operation Shark Fin' to find a patentable replacement. The result was esomeprazole, released in 2001, with four trials showing little difference between the new single enantiomer and its dual enantiomer predecessor omeprazole [32].

The battle for the antacid market throughout the 1990s gave the pharmaceutical industry invaluable commercial lessons. To have one of the most successful commercial products in the world demanded little cutting edge science. The billions of US dollars at stake depended upon incremental changes to the initial scientific breakthrough with me-too drugs. This lowered the market value of ground breaking science and made fortunes for those who understood commerce. The management boards of major companies reflected this change; as a gross generalization, the scientists were out and the marketers were in. The competitive me-too marketplace favours large-scale trials to support marketing campaigns, where there may be little to distinguish drugs of the same class [36], but this consumes a large proportion of the research budget.

Cutting edge science might investigate novel treatments for tropical diseases, but if sales in low income countries cannot recoup the investment then this makes little commercial sense. The antacid market showed that chronic diseases in a large proportion of a wealthy population are the likely source of blockbuster income (defined as over $1 billion per year) and the top 10 selling drugs worldwide reflect this. Chronic treatment of common conditions, such as cardiovascular risk factors, asthma or psychiatric symptoms makes financial sense. To recoup investment requires chemical, manufacturing, sometimes device and use patents. This makes the funding of the investigation of old generic drugs for new indications unattractive, unless a new use patent is generated. The study of spironolactone for heart failure [37] is one example that was difficult to fund because it did not generate a new use patent (Bertram Pitt, personal communication).

Marketers can create a large-scale desire for a soft drink or hair conditioner and this approach adapts well to medicines. Successful campaigns increased the diagnosis rate of juvenile bipolar disorder 40-fold in the USA between 1993 and 2004 [38]. Sales teams have proposed that more than one in five of the population suffer from many conditions – pre-hypertension, too much cholesterol, excess weight, metabolic syndrome, fatty liver, anxiety, insomnia, sadness, fibromyalgia, interstitial cystitis, irritable bowel syndrome, hyperactivity, sexual malfunction or restless legs – and need appropriate long-term medicines for each. Before taking drugs for any of these it is worth recalling visceroptosis, a condition of mobile internal organs requiring surgical re-attachment [39] that did not go out of fashion until the 1940s.

It is commercial reality that medicines innovation includes many clever advances in marketing techniques. These need to be acknowledged, as they pay the cost of much basic research. When marketing innovation and drug discovery expertise diverge, then the two need to be separated and goals for each defined. Most pharmaceutical companies recognize this and encourage collegiate style grouping of basic researchers, recognizing the unpredictability of future commercial success at early stages of development.

National interests are not the same as public good. It is wise for a nation to encourage an active pharmaceutical industry. If public health were the only motivation, then 80% of cardiovascular disease is preventable by the simplest non pharmacological measures [40], as are over 70% of cancers [41].

Conclusions

Despite the absence of genetic inheritance and mutation, the drug discovery process has many parallels with evolution. The selection process has multiple extinctions at each stage of development and few molecules survive to market. As the ability to generate variation with new molecules increases with advances in science, the recent increase in the extinction rate needs to be explained.

Lack of funds does not delay drug discovery; spending in recent years has gone up and productivity is down. The money spent on pharmaceutical research exceeds the Gross Domestic Product of many countries. Historically many successful compounds were found by groups of less than 50 scientists, small compared with many industry groups today.

The Red Queen hypothesis has a parallel in innovation in that advances in science that detect potential efficacy will also lead to greater understanding of potential safety concerns. As science advances, so regulation must follow. The expertise of the regulator should match that of the innovator if safe, effective medicines are to be made rapidly available. The current record high rate of approval suggests that red tape is not killing innovation, the problem is the fall in the number of applications for authorization. The modern trend to contract out studies, requiring lengthy legal international negotiations, has hindered the ability to conduct a logical series of small scale clinical experiments. 'White space', a term common in industry to describe time lost in contract negotiations, has taken a heavy toll on mechanistic studies, the crucial part of drug development. More effort is needed to resuscitate phase 2 studies. Enthusiasm for adaptive designs, where the contracted trial protocol is modified during the study to take into account the study's interim results, has not compensated for the commercial pressure to rush from phase 1 to phase 3.

Given their impact on the field, it is surprising that stars such as Elion, Black and Endo, though awarded prizes and still recognized [42], are not promoted more often as role models. Their achievements are rarely celebrated and their expertise in chemistry not widely recognized.

Two external impacts had a profound effect on the field. The Berry Plan accelerated the expansion of clinical pharmacology that started in the 1940s, but this stimulus needs a replacement. Heavy funding of genetics has produced many advances, but also diverted money away from research into new therapeutic chemical entities. It is important to support the triad of chemistry, pharmacology and clinical pharmacology on which drug discovery depends [25], together with the expansion of biology.

Patents are the collateral that allows investment in drug development. Though academia has jumped into the patent pool often one institution at a time, a collective approach to technology transfer could be more cost effective for universities. The patent system would benefit from simplification, particularly from better international coordination.

The different philosophies of marketing and science need to be acknowledged, each recognizing the strengths of the other, but with greater separation of the two. The top 10 drugs that are useful to society do not overlap with the top 10 of the commercial hit parade. This is no surprise given the patent system, but the goals of any innovation programme need careful definition.

Better value could be obtained for the money spent on medicines research by the favourable manipulation of the forces that apply to the process of discovery.

Competing Interests

There are no competing interests to declare. Although the author has worked for regulatory authorities, the views expressed are his own and do not reflect those of any agency or institution.

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